REMARKS

Claims 23-35 and 66-75 were pending in this application. Claims 23 and 66 are hereby amended. Claims 28-31 and 72 are cancelled. Claims 25-27, 32-35, 66-71, and 73-75 are now pending.

Support for these amendments exists throughout the specification as filed. More specifically, support exists at page 2, line 15, which states: "This invention provides prolonged local retention of therapeutic agent activity in the airways for use with selected therapeutic agents in managing pulmonary disease." Support also exists on page 24, line 21 which reads: "Pulmonary drug delivery is also advantageous for local treatment of the lung in that it promotes an increase in drug retention-time in the lung and more importantly, a reduction in extra-pulmonary side effect, invariably resulting in enhanced therapeutic efficacies (Shek, 1994)." Page 24 line 30 reads: "The use of in vivo or ex vivo bioconjugation associated with pulmonary drug delivery includes the following non-limited benefits. Retention of the drug at the site of placement is enhanced due to covalently attachment of the drug to the airway site. Additionally, prolonged activation of the drug is made possible, ...in the lung by in situ attachment to soluble proteins for localized intrapulmonary activity..."

Restriction

Applicants acknowledge the restriction requirement has been made final. Applicants reserve the right to pursue the non-elected claims in related applications.

Rejection under 35 U.S.C §102(b)

The Examiner has rejected claims 23-24, 26-27, 66-67, 69-70, and 72 as being anticipated by WO 98/00171, hereafter referred to as the Krantz, et al. reference. Krantz et al.

discloses, in the Examiner's words: "...treatment with compounds comprising chemically reactive derivatives of a thrombin inhibitor that can react with available reactive functionalities on blood components to form covalent linkages (abstract). Treatment with the conjugate to various blood components is disclosed (page 10 lines 17-21). Serum albumin and platelets, which applicants disclose [page 20, lines 4-31] as both a mobile and stationery pulmonary and blood components, is specified (page 5 line 28). Hydroxysuccinimide is disclosed (page 7 line 13). An aerosol is specified (column 11, line 230)."

Claim 23 as amended now reads: "A method of delivering a therapeutic agent to a host comprising the steps of: obtaining a modified therapeutic agent, the modified therapeutic agent comprising the therapeutic agent and a reactive group which reacts in vivo with an amino group, hydroxyl group or thiol group on a fixed pulmonary component to form a stable covalent bond; and administering the modified therapeutic agent to the pulmonary system of the host, **wherein said therapeutic agent covalently bonds to the fixed pulmonary component and is not transferred to the vascular system.**" (Emphasis added.) A similar amendment has been made to claim 66. The Krantz et al. reference does not teach or suggest that the therapeutic agent bonds to a fixed pulmonary component and is not transferred to the vascular system. On page 11, lines 18-24 of the Krantz et al. reference, the following is stated:

> "The subject derivatized thrombin inhibitors will for the most part be administered parenterally, such as intravascularly (IV), intraarterially (IA), intramuscularly (IM), subcutaneously (SC), or the like. Administration may in appropriate situations be by transfusion. In some instances, where reaction of the active functional group is relatively slow, administration may be oral, nasal, rectal, transdermal or aerosol, **where the nature of the conjugate allows for transfer to the vascular system.**" (Emphasis added.)

Krantz et al, does teach the use of aerosol administration for transfer of a conjugate to the vascular system. There is no teaching that the conjugated peptides are bonded to fixed pulmonary components and not transferred to the vascular system. In light of these arguments and amendments, Applicants assert that the Krantz, et al. reference does not anticipate independent

claims 23 or 66 as amended, and therefore also does not anticipate the rejected dependent claims. Applicants respectfully request the withdrawal of this ground of rejection.

Rejection under 35 U.S.C §102(b)

The Examiner has rejected claims 23-24, 26-32, 66-67, and 69-72 as being anticipated by WO 99/24462, hereafter referred to as Bridon, et al. Bridon et al. discloses, in the Examiner's words: "...treatment using a derivative of an RGD containing peptide including a reactive functional group. The compound or its conjugate can be administered (abstract). Maleimide is disclosed (page 9 line 28). An aerosol is specified (page 12 line 22). Serum albumin and red blood cells are disclosed (page 11 line 28-page 12 line 4)."

As stated above, Claim 23 as amended now reads: "A method of delivering a therapeutic agent to a host comprising the steps of: obtaining a modified therapeutic agent, the modified therapeutic agent comprising the therapeutic agent and a reactive group which reacts in vivo with an amino group, hydroxyl group or thiol group on a fixed pulmonary component to form a stable covalent bond; and administering the modified therapeutic agent to the pulmonary system of the host, **wherein said therapeutic agent covalently bonds to the fixed pulmonary component and is not transferred to the vascular system.**" (Emphasis added.) A similar amendment has been made to claim 66. Bridon et al. does not teach or suggest that the therapeutic agent bonds to a fixed pulmonary component and is not transferred to the vascular system. On page 12, lines 16-23 of the Bridon et al. reference, the following is stated:

> "The subject RGD peptide derivatives will for the most part be administered parenterally, such as intravascularly (IV), intraarterially (IA), intramuscularly (IM), subcutaneously (SC), or the like. Administration may in appropriate situations be by transfusion. In some instances, where reaction of the active functional group is relatively slow, administration may be oral, nasal, rectal, transdermal or aerosol, **where the nature of the conjugate allows for transfer to the vascular system.**" (Emphasis added)

Bridon et al, does teach the use of aerosol administration for transfer of a conjugate to the vascular system. There is no teaching that the conjugated peptides are bonded to a fixed pulmonary component not transferred to the vascular system. In light of these arguments and amendments, Applicants assert that Bridon, et al. does not anticipate independent claims 23 or 66 as amended, and therefore also does not anticipate the rejected dependent claims. Applicants respectfully request the withdrawal of this ground of rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 23-27, 66-70, and 72 as being unpatentable over the Bridon et al. reference in view of Edwards et al. (US 5,874,064). The Examiner has also rejected claims 23-33 and 66-72 as being unpatentable over Krantz et al. in view of Edwards et al. Specifically, the Examiner states: "It would have been obvious to one of ordinary skill to use the Edwards, et al. particulates in the treatments of WO '462 and WO '461 to achieve the beneficial effect of enhanced delivery." After a phone call with the Examiner, Applicants confirmed that "'461" should have been "'171", the Krantz et al. reference.

In order to make a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP 2142). Applicants contend that Bridon and Edwards or Krantz and Edwards, when combined, do not teach or suggest all of the claim limitations. Specifically, the references when combined do not teach or suggest the limitation of "**wherein said therapeutic agent covalently bonds to the fixed pulmonary component and is not transferred to the vascular system.**" as claimed in independent claims 23 and 66, as amended. (emphasis added)

Neither Krantz, et al. nor Bridon, et al. teaches or suggests this limitation. Edwards, et al. teaches, according to the Examiner "...inhalation of particulates comprising a therapeutic agent for enhanced delivery (abstract). Any of a variety of actives is disclosed, including peptides (column 10 lines 1-5)." Edwards, et al. does not teach use of a therapeutic agent which bonds to a

pulmonary component and is not transferred to the vascular system. Therefore, neither Krantz et al., nor Bridon et al., nor Edwards et al., alone or in combination, teach or suggest the claim limitation of "wherein said therapeutic agent bonds to the pulmonary component and is not transferred to the vascular system." Applicants contend that the Examiner has not made a *prima facie* case of obviousness against any of the rejected claims, as there is no teaching in the combination of the cited references of the claim limitation of "wherein said therapeutic agent bonds to the pulmonary component and is not transferred to the vascular system."

The second criterion of a prima facie case of obviousness is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Krantz and Bridon, as discussed above, disclose therapeutic peptides which can be conjugated to blood components for increased half life in the blood. Edwards, et al. teaches the formation of aerodynamically light particles which can help in pulmonary delivery of therapeutic agents. There is no suggestion or motivation to combine these two modes of delivery into the body. Aerodynamically light particles have nothing to do with covalent bonding to pulmonary components. Even if these references were combined, the end result would be pulmonary delivery of a therapeutic peptide and transfer of the therapeutic peptide to the vascular system. Therefore, there is no suggestion or motivation in the references cited, either alone or in combination, to deliver a therapeutic agent, "wherein said therapeutic agent covalently bonds to the fixed pulmonary component and is not transferred to the vascular system."

The third criterion of a *prima facie* case of obviousness is that there must be a reasonable expectation of success. As discussed above, the combination of the peptides of Krantz or Bridon with the aerodynamically light particles for delivery from Edwards, would lead to pulmonary delivery of a therapeutic peptide and transfer of the therapeutic peptide to the vascular system. There is no reason to expect that the therapeutic peptide would bond to a fixed pulmonary component and not be transferred to the vascular system as both Krantz and Bridon describe delivery to the vascular system.

Based on the above, Applicants respectfully provide that a *prima facie* case of obviousness has not been made, and request the rejection of independent claims 23 and 66, and dependent claims 24, 67, 69 and 70, be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 33-35, 73-75 because "...the specification, while being enabling for the compounds of examples 17 and 18, does not reasonably provide enablement for any antihistamine."

The specification provides methods for synthesizing a wide array of peptides, including antihistamines that are protected from protease degradation by the addition of a reactive group and subsequent conjugation to a blood or pulmonary component. The specification provides clear instructions for choosing the site at which the peptide should be modified, which reactive groups can be used, and what blood or pulmonary components are available. Upon reading the present specification, one of skill in the art would be able to take any therapeutic agent of interest and create an agent protected against peptidase activity. There are numerous examples of therapeutic agents given in the specification, including antihistamines, but the description is not limited to these specific embodiments. Rather the specification teaches a general method of stabilizing therapeutic agents which is applicable to all antihistamines.

Therefore, based upon the teachings of the present application Applicants submit that one of skill in the art would be able to take any antihistamine and create an antihistamine protected against peptidase activity. Even if a specific antihistamine was not described in the specification, one of skill in the art would be able to practice the invention and create an antihistamine protected against peptidase activity. Applicants submit that the specification meets the written description requirement and request withdrawal of this rejection.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 500862001810. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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